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ON ELECTROKINETIC PHENOMENA AT BIOLOGICAL SURFACES

WITH SPECIAL CONSIDERATION OF THE RED BLOOD CELLS

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ABSTRACT. The electrical charge and field strength
at the cell membrane of human erythrocytes are determined
and their importance for modern diagnostics stressed.
Each red blood cell carries about 8000 elementary charges
at the membrane surface.

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SUMMARY

Electrokinetic processes at limiting surfaces are a commonly occurring
phenomenon in animate and inanimate nature. They have particular significance
at biological surfaces as energy reservoirs for certain processes.

In general, information exchange between the living cell and its
environment proceeds by means of the surface charge of the cell membrane [14].
The cell membranes receive (through charge changes), store (with their double
layer capacity) and convert the arriving informational energy into chemical
energy. This informational energy can be of biochemical (nutrients, hormones,
etc.) or physical nature (external force fields, such as electrical and magnetic
fields or the gravity field). These effects produce ion concentration gradients
and thus potential differences at the cell membrane surface: Thus the informa-
tion exchange between the living cell and its environment is electrochemical in
nature, running its course at the boundary surface between the cell and the
surrounding milieu.

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*Numbers in the margin indicate pagination in the original foreign text.

Human blood fulfills many essential functions, and can be called a liquid organ. In every cubic millimeter of blood there are suspended some five million red blood cells carrying a negative electrical charge. This work represents an attempt to determine the amount of the charge and the field strength appearing at the cell membrane surface of a red blood cell on the basis of the well-known geometrical configuration of human erythrocytes. It was found that each red blood cell carries approximately 8,000 elementary negative charges at its membrane surface. Apparently the stability of the blood suspension is also maintained in this way.

The significance of the erythrocyte surface charge for modern diagnostics is not to be underestimated. Numerous biochemical and biophysical processes are detectable through alterations in charge, especially with variations of the pH value or of the ionic strength of the blood. Various environmental factors also affect the surface charge of blood cells, as, for example, air pressure, temperature, certain electromagnetic vibrations, and especially high-energy radiations.

In theory, fields stronger than 134 V/cm must produce a measurable charge displacement at erythrocyte membranes, thus distorting their function in gas transport and exchange. How broadly this idea applies will be shown in the course of further investigation.

A. INTRODUCTION

Electrokinetic phenomena at boundary surfaces occur in animate and inanimate nature. They are decisive for a large number of biophysical and biochemical mechanisms. A diffusion barrier arises due to various inter- /2 molecular forces at two different phases. Thus layers of electrical charge carriers form — electrons, ions and electrical dipoles — because almost all molecules either have a polar electrical structure or carry free charges as ions. Then a certain arrangement of the particles appears, followed by directed electrical forces. In this way the electrical double layer originates [1].

The electrical double layer always appears at the boundary surface between two stationary phases with different chemical and physical properties, whether these phases are organic or inorganic. The state of aggregation also has no effect. This is shown by numerous examples in nature. Fog and smoke owe their existence solely to the electrical charge at the surfaces of their particles. The particles repel each other because of their similar electrical charge, and so remain homogeneously distributed in space. Our globe forms an electrical double layer with the atmosphere. It appears at the boundary surface of a solid phase (Earth) and a gaseous phase (atmosphere). The total electrical charge of one layer, the Earth, amounts to some $0.5 \cdot 10^6$ ampere-hours. Cloud masses with different temperature and mobility develop surface charges as gas-gas limiting surfaces. There is a charge exchange through lightning strokes, in which there develops an average potential of $0.3 \cdot 10^6$ V and a current of about $0.1 \cdot 10^6$ A. Inorganic particles such as quartz in a liquid also show a negative charge of their surface with respect to the liquid. Boundary layer phenomena between two different solid phases are extensively studied in physics. They find their broadest application in electro-technology, as, for example, semiconductor effects for diodes and transistors, thermo-pair effects in measurement technology, or through the inverse, so-called, Peltier effect for cooling devices.

Electrode potentials play a wider role as a result of boundary layer phenomena. They arise if an electrode of conductive material is dipped into a liquid (electrolyte). A potential difference appears between the electrode and the liquid. In measurement of very low currents, as in bioelectricity, this process introduces serious problems, and can lead to falsification of the experimental results.

The full importance of the electrical double layer is not yet comprehensible in medicine. But we realize that these phenomena can represent an energy source for mechanical substitute organs. That is, if we dip two electrodes of different conducting materials, such as metals, into a body fluid (electrolyte) such as urine or blood, a current flows between the electrodes. This electrical energy can suffice to stimulate or activate an

artifical organ, for instance, an implanted electrical pacemaker for heart patients.

Aside from thermal processes, there is also an electrical process taking place in the microclimate surrounding our skin. Contact and friction of body and clothing, as well as between layers of clothing, produce a charge separation, and so a potential difference, and thus a field strength, particularly /3 for clothing made from artificial fibers. With ordinary body movements, the value of this field strength is of the order of magnitude of 100 V/cm, that is, about one-hundred-fold the field strength of the atmosphere. With especially dry air, this value can reach 1,500 V/cm or more, so that sparks up to 5 cm long can occur when the clothes are removed. This indicates that a field strength of over 150 kV/cm prevails in the air. We call this process transverse or radial polarization. In contrast to this, there is head-foot polarization, in which environmental influences are expressed as stimulating effects. We designate this process as longitudinal polarization.

In biological objects and systems, boundary surfaces appear at all places where different tissues come into contact, such as at cell membranes, skin, connective tissue sheaths, capillary membranes, chromosomes, mitochondria, and furthermore, at all visible and invisible boundary layers. The double layer has great significance in biology. Enzyme reactions, and genetic and locational information transfer are presumably coupled with double layer potentials and capacities. The potential differences and voltages which appear at the cell membrane surfaces of bacterial cells, nerve cells, and red blood cells (erythrocytes) due to charge differences are of particular importance. In the following we attempt to calculate these values for erythrocytes.

B. PHYSIOLOGY OF THE ERYTHROCYTES

1. General Consideration of the Erythrocytes

The name "erythrocyte" for the red blood cells is of Greek origin. Erythrocytes are found only in the blood of living vertebrates. They vary in

4

number and size. They obtain their red color from hemoglobin, to which oxygen molecules are bound in the form of iron oxide. Mammalian erythrocytes move in the blood flow. Their physiological function is that of oxygen transfer, i.e., gas exchange between the lungs and tissues. The erythrocytes are non-nucleated cells which do not reproduce, but are formed in the red bone marrow. In humans, there are about five million erythrocytes in one cubic millimeter of blood. These blood cells have no genetic apparatus, and neither nucleoside or protein synthesis occurs in them. Their metabolism is purely glycolytic. That is, to obtain energy they use the chemical energy of a single nutrient, glucose [2]. The total weight of the red blood cells of a human can be calculated in the following way: If we assume that 8% of our body weight is blood, and that 44% of the blood is made up of erythrocytes [8], we obtain the following weight proportion for humans with G kilograms body weight:

$$G_E = 0,08 \cdot 0,44 \cdot G \, (kg)$$

$$\boxed{G_E = 3,52 \cdot 10^{-2} \cdot G \, [kg]} \tag{1}$$

a. For an adult human with a body weight of $G = 70$ kg, the total mass /4 of the blood is

$$G_B = 70 \cdot 0,08 = 5,6 \, kg$$

or, if we consider the specific gravity of the blood, $\gamma_B = 1.1$ [8], we obtain a blood volume of

$$V_B = \frac{G_B}{\gamma_B} = \frac{5,6}{1,1} \approx 5,1 \, \text{Liter}$$

b. For the same person, according to (1), the proportion of erythrocytes to the body weight is

$$G_E = 3,52 \cdot 10^{-2} \cdot 70 = 2,46 \, kg.$$

2. Geometry of the Erythrocytes

The erythrocytes have a circular shape, and resemble a torus more than a sphere (see Figure 1).

Figure 1. Representation of an erythrocyte model. The erythrocytes are non-nucleated, flat, circular cells with a central depression. They have a lifetime of about 4 months.
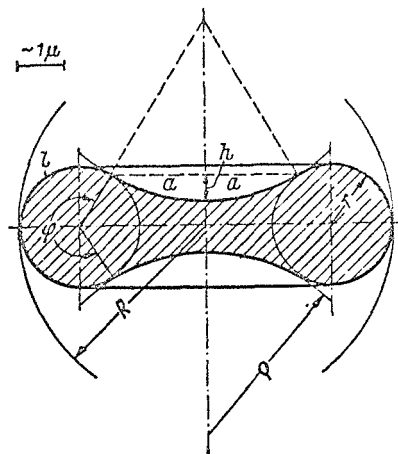

Figure 2. Geometry of the erythrocyte cross section for calculation of the surface area.

We can approximately calculate the surface of the erythrocyte by dividing it into two parts, a torus and a segment of a sphere.

a. Torus (F_1)

The outer surface of a torus can be calculated from the geometrical representation (see Figure 2) as follows:

$$F_1 = 2\pi \cdot R_0 \cdot l$$

$$(2)$$

in which $\quad l = r \cdot \dfrac{\pi \cdot \varphi}{180}$,

For $c = 245°$ and $r = 1.3\,\mu$ it follows that $\quad l = 1,3 \cdot \dfrac{3,14 \cdot 245}{180} = 5,56\,\mu$

6

The mean radius (R_0) for the torus surface is $R_t \approx R - 1 = 4 - 1 = 3\mu$,

Then it follows from (2) that $F_1 = 2\pi \cdot 3 \cdot 5{,}56 \approx 100\,\mu^2$.

    b. Spherical segment (F_2)

From the formula for the surface area of a spherical segment, for

      $h \approx 0{,}6\,\mu$ (measured in Figure 2)

      $\varrho \approx 3{,}9\,\mu$ (measured in Figure 2)

it follows that

$$F_2 = 2\pi\varrho h = 6{,}28 \cdot 3{,}9 \cdot 0{,}6 = 14{,}7\,\mu^2.$$

Then the total surface area is

$$F = F_1 + 2F_2 = 100 + 2 \cdot 14{,}7 = 129{,}4 \approx 130\,\mu^2.$$

From this surface $(130\,\mu^2)$ we obtain by means of the formula for the surface of a sphere, $F = 4\,\jmath r^2$, the so-called reduced radius (R_r). This is the radius /6 of the sphere with which we could approximately replace the erythrocyte.
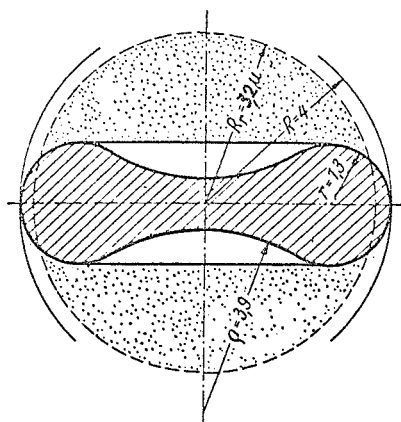
Thus: $$130 = 4\pi R_r^2$$

or

$$R_r = \sqrt{\frac{130}{4\pi}} = \sqrt{10{,}3} \approx 3{,}2\,\mu.$$

Figure 3 represents this sphere with the reduced radius (R_r).

3. Development of Electrical Potentials at the Erythrocyte Surface

In general, the electrical potential difference at boundary surfaces of porous membranes, which includes the biological membranes, consists of two component potentials, namely

1) the potential difference between the two sides of the membrane (Donnan potential) and

2) the potential difference between one side of the membrane and the surrounding medium (Helmholtz layer).

Figure 3. Cross section of an erythrocyte, and of a sphere replacing the erythrocyte, having the radius $R_r = 3.2\mu$ instead of $R = 4\mu$.

1. The potential gradient between the inner and outer sides of the cell membrane arises from the continuous movement of ions in both directions (dynamic equilibrium). Also, the concentration of cations and anions (see Table I) on both sides of a semipermeable membrane cannot be the same, because the concentration of proteins

TABLE I. DISTRIBUTION OF INORGANIC COMPONENTS BETWEEN BLOOD PLASMA AND ERYTHROCYTES (ACCORDING TO STRAUB [12], PAGE 544).

Ion	Milliequivalents per liter of water	
	Plasma	Erythrocytes
Na	120 — 150	10 — 27
K	4 — 6	95 — 110
Ca	4,5 — 5,5	0,25 — 1,0
Mg	1,5 — 1,8	3,5 — 4,5
Cl	90 — 110	40 — 60
HCO_3^-	23 — 33	13 — 18

is greater on one side than on the other [12]. For this reason, a potential difference appears at the cell membrane from diffusion of the ions. This can be demonstrated by means of a simple experiment with erythrocytes. If blood is allowed to cool in a test tube, potassium leaves the erythrocytes through the membrane. On an increase in temperature, the potassium returns to the cells. If glucose is added to the blood, the loss of potassium is delayed, and the uptake accelerated, depending on the requirement. As the potassium leaves the cell, as a rule sodium diffuses in the opposite direction. This indicates that /7 the erythrocytes maintain their high potassium concentration only through their metabolic process, in which the catabolism of carbohydrates plays the major role [3]. The mobility, size, and concentration of the ions at the cell membranes are different. For this reason a diffusion potential appears at the membrane surface. Table I gives a comparison of the ion concentration of blood serum and the red blood corpuscles.

The Na^+ and K^+ concentrations show the most striking inequality in cation distribution. The blood plasma shows a high Na^+ and a low K^+ picture; in the red blood cells, by contrast, there is a high K^+ and a low Na^+ concentration. It appears as if the erythrocyte cell membrane were impermeable to cations; but experiments performed with isotopic ions show that both K^+ and Na^+ ions can penetrate the cell wall. Numerical evaluation of the results shows that in dynamic equilibrium 1.7 milliequivalents of K^+ ions diffuse in both directions through human erythrocyte membranes per hour and liter. The energy-yielding process of glycolysis provides for the maintenance of the high K^+ concentration of erythrocytes in relation to the plasma.

Through diffusion, the K^+ migrates from the location of higher concentration outward, and Na^+ inward, but simultaneously K^+ and Na^+ also move from low concentration levels to higher ones by means of glycolytic energy (active transport). It is generally assumed that cell work is required for the outward transport of Na^+, so that this phenomenon is called the sodium pump. In order to maintain the electrical neutrality of the cell, K^+ ions then migrate from the blood plasma to the cells.   /8

For membrane potentials in general, we can follow the deliberations of Nernst: Under normal conditions, and if the mobility differences between the ions on both sides of the cell membrane are not too great, this potential can be represented mathematically in simplified form as:

$$U_m = 59{,}1 \cdot \log \frac{C_1}{C_2} \left[mV \right] \tag{3}$$

This is the so-called Nernst equation for the Donnan potential. Let us take as an example the potential between blood plasma and erythrocytes due to the concentration difference of Na^+ ions. From Table I, we obtain the ion content of the plasma as $C_1 \approx 150$ milliequivalents and that of the erythrocytes as $C_2 \approx 15$ milliequivalents.

Thus we obtain $\dfrac{C_1}{C_2} = 10$. From this it follows that $U_m = 59.1$ mV.

This potential is negative on the outside. This does not apply, however, for the excitation potential of nerve cells.

2. The negative excess charge at the outer side of the cell membrane attracts the positively charged ions as well as dipolar molecules, such as water and protein molecules. From these dipoles and positive ions there forms a cloudlike counter-layer (see Figure 5). These two layers, the negative one on the membrane surface and the positive counterlayer which is formed, are called the electrical double layer or, from the name of the discoverer, the Helmholtz layer. The electrical double layer plays a great role in metabolism and information exchange of the cell. The carboxyl group (-COOH) of the neuraminic acids as well as the pH value and the current ionic strength of the blood are the decisive participants in production of the electrical double layer [1].

Thus, for example, the following forces act on the surface of a red blood corpuscle in suspension at equilibrium (Figure 4):

$$P = P_o + P_c$$

10

where

$$P = \text{electrolytic solution pressure}$$
$$P_o = \text{osmotic pressure}$$
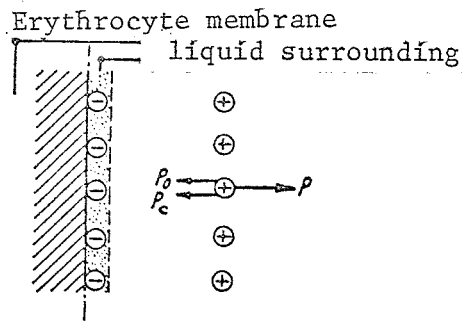$$P_c = \text{electrostatic attraction force.}$$

Figure 4. Development of a steady equilibrium condition in the double layer through the action of the three forces (P, P_o and P_c)

The potential gradient is the greatest at the beginning of the double layer formation, since the counter-pressure (P_0) is approximately zero. As soon as the ion density increases, the potential gradient diminishes, as the counter-pressure (P_o) is greater and fewer ions can leave the membrane surface. This explains the fact that the increase of ion density in the solution decreases the potential difference of the surface. This process continues only until the so-called steady state is reached; that is, until the electrical field developing within the double layer has become so strong that binding of more positive ions is prevented.
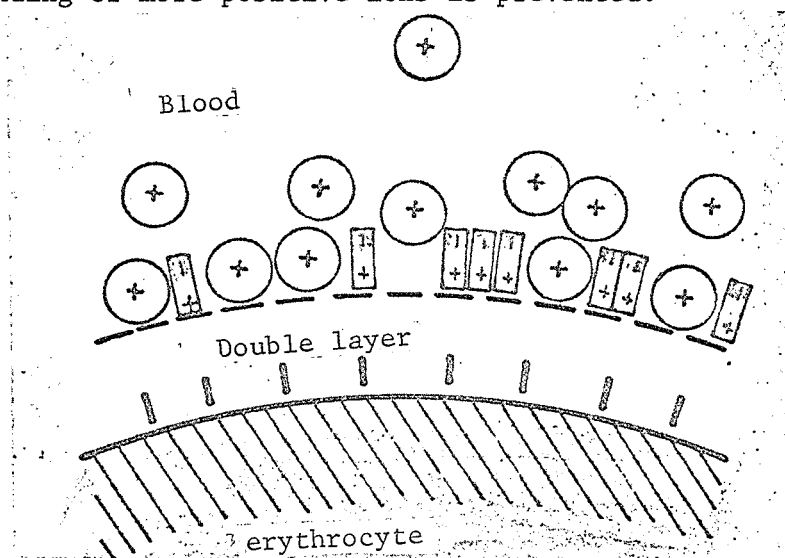

Figure 5. Schematic representation of the electrical double layer around an erythrocyte, consisting of negative charges on the membrane surface and of positive ions and dipoles in the blood.

As long as the resulting negative charge on the membrane surface is
constant, and with a given ion concentration for the solution, the positive ions
of the double layer can change their positions but not their number. A liquid
layer adheres to the cell membrane surface and moves along with the membrane
if the cell moves through the solution. If the strength of the double layer
exceeds the strength of the liquid layer (x) (see Figure 6) there arises a
potential difference between the membrane and the buffer. But if the strength
of the double layer is reduced to or even
below that of the liquid layer (x) by an
increase in the ion concentration of the
liquid, no potential difference appears,
as the distance between the ions is too
slight, so that the arrangement of the
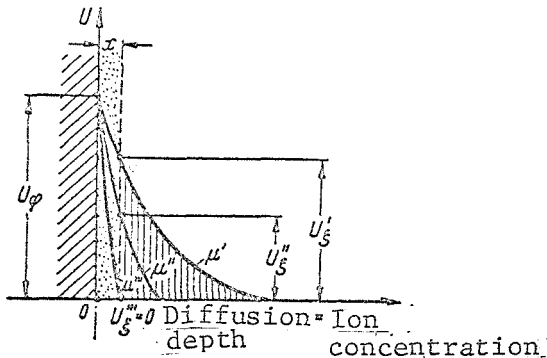double layer is destroyed by inter-
molecular forces.

Figure 6. Potential curve (U') for
a certain ionic concentration in
the solution (µ') as a function of
the distance. The potentials
appear only beyond a certain dis-
tance (x).

It can be seen from Figure 6 that
different potentials correspond to dif-
ferent ion concentrations (µ', µ", µ''')
at the surface of the water envelope.
According to Freundlich and Abramson [10],
under normal conditions this potential
has an average value of 27 mV for erythrocytes.

The potential difference between such electrical layers — the electrical
excess charge — as well as the capacity of an erythrocyte is treated in the
following sections.

4. Electrical Capacity (C) of the Double Layer.

A sphere of known radius (Figure 7) is taken as an analogous model of
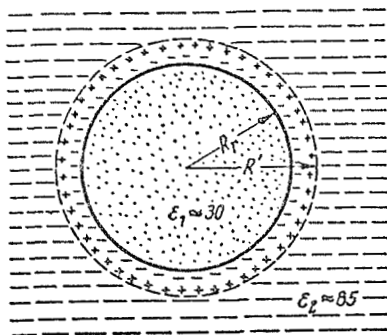the erythrocyte.

12

Figure 7. Erythrocyte in buffer, with the resulting electrical double layer around it, to be considered approximately as a spherical capacitor.

The general formula for the electrical potential is

$$U = \int_{R_1}^{R_2} E\,dr$$

and for the electrical field at a spherical surface we have

$$E = \frac{1}{4\pi\varepsilon} \cdot \frac{Q}{r^2} \qquad (4)$$

Then it follows that

$$U = \frac{Q}{4\pi\varepsilon}\left(\frac{1}{R_r} - \frac{1}{R'}\right) = \frac{Q}{4\pi\varepsilon_0 \cdot \varepsilon_r} \cdot \frac{R' - R_r}{R' \cdot R_r} \qquad (5)$$

From $U = \dfrac{Q}{C}$ it follows that

$$C = \frac{Q}{U} = 4\pi\varepsilon_0 \cdot \varepsilon_r \cdot \frac{R' \cdot R_r}{R' - R_r} \qquad (6)$$

If we note that

$$4\pi\varepsilon_0 = 4 \cdot 3{,}14 \cdot 8{,}856 \cdot 10^{-14} = 1{,}11 \cdot 10^{-12}\ \text{F/cm}$$

13

then we can derive

$$C = 1{,}11 \cdot \varepsilon_r \cdot \frac{R' \cdot R_r}{R' - R_r} \quad [pF]$$

(7)

Since the radius of the outer layer is unknown, we must assume that R' is <u>/12</u> infinitely distant. This, based on formula (5), gives this expression for the capacity:

$$C = 1{,}11 \cdot \varepsilon_r \cdot R_r \quad [pF]$$

(8)

This is the capacity of an isolated smooth spherical surface. If we insert the appropriate values for q = 85 and R_r = 3.2 μ, then according to (8) we obtain

$$C = 1{,}11 \cdot 85 \cdot 3{,}2 \cdot 10^{-4} \approx 3 \cdot 10^{-2} \quad [pF].$$

But since the surface of erythrocytes is not smooth, but rough (see Figure 8), we multiply this value by an estimated factor of 2, so that we now have

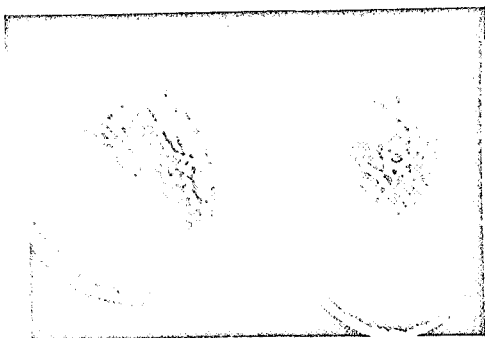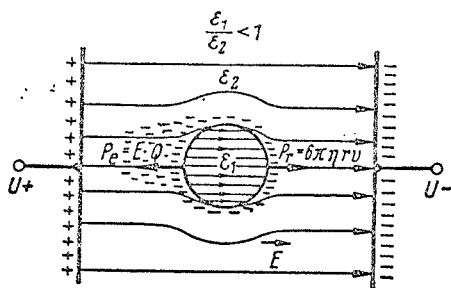$$C = 2 \cdot 3 \cdot 10^{-2} = 6 \cdot 10^{-2} \; pF.$$

Figure 8. Fine structure of human red blood cells, proving that the erythrocytes do not have a smooth surface, but a rough one. In this way, their capacity is increased, as for etched metal foils. The capacity is probably increased by a factor of 2. (Photograph by Lewis, Osborn and Stuart, London, 1969).

14

5. Excess Charge (Q) of the Erythrocyte Membrane

Figure 9. The electric force (P_e) arising from the excess charge (Q) and the Stokes frictional force (P_r) as an expression of two forces acting in opposite directions on the erythrocytes

If a direct current flows, the electrical double layer of the erythrocyte will undergo a tangential distortion. that is, the negative blood corpuscle moves — becoming displaced in the positive pole (Figure 9) [11].

In order for the erythrocyte to move and migrate in the electrical field (E) there must be equilibrium between the electrical force of attraction and the Stokes frictional force (see Figure 9):

$$EQ = 6\pi\eta r v \tag{9}$$

If we wish to express the electrical force in dynes, we can write

$$1\,\text{Wsec} = 1\,\text{Coulomb} \cdot 1\,\text{Volt} = 3 \cdot 10^9 \cdot \frac{1}{300} = 10^7\,\text{erg or}$$

$$\frac{1\,\text{Ws}}{\text{cm}} = 10^7\,\text{dyn}.$$

Thus we obtain $EQ \cdot 10^7 = 6\pi\eta r v$. For $B = \dfrac{V}{E}$ it follows that

$$Q = 10^{-7} \cdot 6\pi\eta r \cdot B \; [\text{As}] \tag{10}$$

If we substitute in (10) the values for
- viscosity of the suspension at 20° C, $\eta_k = 1.65$ cP (according to Seaman [9])
- mean radius of the erythrocyte, $r = 4 \cdot 10^{-4}$ cm
- electrophoretic mobility at 20° C

15

$$B = \frac{v}{E} = 1{,}05 \quad \frac{cm^2}{V\ sec}$$ (see Figure 11)

we obtain the amount of the electrical excess charge of the erythrocyte
according to (10). $Q = 10^{-7} \cdot 6 \cdot 3{,}14 \cdot 1{,}65 \cdot 10^{-2} \cdot 4 \cdot 10^{-4} \cdot 1{,}05 \cdot 10^{-4} = 1{,}3 \cdot 10^{-15}$ As.
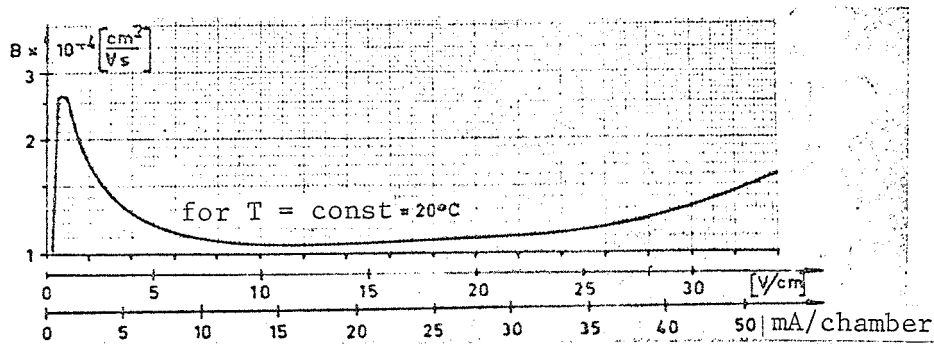

Figure 10. Effect of the current strength (I) through a measuring chamber with
a cross section of q = 0.097 square centimeters, or a calculated field strength
in the chamber of $E_k = \varrho\ I/q$, on the electrophoretic mobility (B) of human
erythrocytes suspended in a 0.9% solution of sodium chloride (pH = 6.96,
$\varrho = 70\ \Omega$ cm). The curve is linear in the range from 10 to 24 V/cm, and then
rises gently.

From this there follows the number of elementary charges:

$$n = \frac{Q}{e} = \frac{1{,}3 \cdot 10^{-15}\ As}{1{,}6 \cdot 10^{-19}\ As} = 8125 \text{ elementary charges}$$

Beier [5] has obtained almost the same value, 7,870 elementary charges,
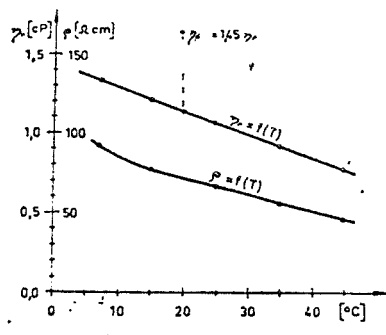according to a different method.

Figure 11. Within the temperature range
between 10° C and 45° C, the relative
dynamic viscosity of the suspension y
has a curve almost parallel with that of
the specific resistance z. Thus the
electrophoretic mobility quotient (B)
also does not change in this temperature
range. Because of the capillary effect in
the measuring chamber, the relative visco-
sity increases by a factor of 1.45.

16

This surface charge is practically unaffected by temperature in the range from 10 to 45° C, as the viscosity and specific resistance have almost parallel curves (see Figure 11) and the mobility quotient remains constant. Erythrocytes centrifuged and suspended in 0.9% sodium chloride solution, as well as those treated with sodium citrate, showed no visible difference in electrophoretic mobility, as compared to untreated red blood cells.

The adult human of about 70 kg has a total blood mass of some 5.6 kg or 5.1 liters. The erythrocyte content per cubic millimeter of blood is about 5 million. In the total human blood system, then, there flows in different directions a total electrical current of about

$$\overline{Q} = 5{,}1 \cdot 10^6 \cdot 5 \cdot 10^6 \cdot Q = 25{,}5 \cdot 10^{12} \cdot 1{,}3 \cdot 10^{-15} = 33{,}1 \cdot 10^{-3} \, \text{As charges}$$

or a current of

$$I = \frac{\overline{Q}}{t} = \frac{33{,}1 \cdot 10^{-3} \, \text{As}}{1 \, \text{sec}} = 33{,}1 \, \text{mA.}$$

6. Potential Within the Double Layer, U_D

By means of the effective charge by means of which the movement of the cell in the suspension occurs, we calculate the potential within the double layer according to (6).

$$U_D = \frac{Q}{C} = \frac{1{,}3 \cdot 10^{-15}}{6 \cdot 10^{-14}} = 21{,}6 \, \text{mV.}$$

This agrees in order of magnitude with the results of Freundlich and Abramson [10].

7. Electrical Field (E_m) at the Membrane Surface.

At the distance R_r from the center of the erythrocyte (abstracted as a sphere in this case) we obtain the following value according to (6):

$$E_m = \frac{1}{4\pi \cdot \varepsilon_o \cdot \varepsilon_r} \cdot \frac{Q}{R_r^2} =$$

$$\frac{1}{1{,}11 \cdot 10^{-12} \cdot 85} \cdot \frac{1{,}3 \cdot 10^{-15}}{10{,}3 \cdot 10^{-8}} = 133{,}7 \, \left[\frac{V}{cm}\right]$$

17

This value is about one hundred times the electrostatic field prevailing in the free atmosphere. The electrocytes fulfill their function under these, i.e., the normal, electrokinetic conditions. If the ideas and calculations above agree with reality, this would indicate that the function of the erythrocytes could be positively or negatively affected with a field strength greater than 134 V/cm. This work also demonstrates that even a biological object can be considered physically and can allow exact mathematical calculations as a model.

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